PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2006/004773	19.05.2006	20.05.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/36 A61K38/36

Applicant
ABLYNX NV

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Chakravarty, Ashok Telephone No. +49 89 2399-8536

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/004773

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-78 (part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-78 (part)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1 and 2 partially

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV

The application lacks unity as required by Art. 3(4)(iii) PCT and Rule 13 PCT:

Rule 13.1 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept.

The common concept (technical relationship) linking the presently claimed subject-matter together is the concept "nanobodies* directed against vWF".

However, this concept cannot be regarded as the "single general inventive concept" required by Rule 13.1 PCT because it is neither novel nor inventive, since such antibodies were already known in the art, see WO2004062551 (D1) and WO0024781 (D2), especially the claims.
D1 discloses single domain antibodies directed against any of vWF, vWF A1 domain, A1 domain of activated vWF, vWF A3 domain.
D2 (claim 5) discloses an antibody that binds selectively to the active conformation of human von Willebrand Factor (vWF) and wherein said antibody inhibits the binding of vWF to platelets (claim 1) and wherein said antibody may be a single chain variable region immunoglobulin (ScFv) fragment (claim 2).

Since no other "special" technical feature (Rule 13.2 PCT) could be identified to provide a linking concept each structually distinct embodiment, as set out in the Groups below, must be regarded as a separate invention.

Groups of invention

1: Claim 1-2 (part) directed to a "nanobody" against VWF as defined in claim 1 in which CDR 1 comprises NYGMG (SEQ ID 15), CDR2 comprises "SISWSGTYTAYSDNVKG" (SEQ ID NO 23) and CDR 3 comrises "QSRYRSNYYDHDDKYAY" and related subject-matter .

2-7: Claim 1- 78 (all part) directed to a "nanobody" against VWF as defined in claim 1 in which CDR 1 comprises SEQ IDs 16-22, respectively.

8-33: Claims 21-78 (all part) directed to a "nanobody" consisting of SEQ ID NOS 60-73 or

86-97, respectively

Search is carried out for the 'invention' first mentioned in the claims (Group 1).

Re Item V.

1 Reference is made to the following documents:

D1: WO2004062551
D2: WO0024781
D3: WO2004041862
D4: WO2004041863
D5: WO2004041865

2. The application relates to "nanobodies" against vWF consisting of 4 framework regions and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which each CDR is defined by a sequence recited in the claim.

Although the term "nanobodies" is unclear as it has no generally recognised meaning in the art, the search is carried out under the assumption that the term means antibodies devoid of light chains such as camelid antibodies.

D1 discloses single domain antibodies directed against any of vWF, vWF A1 domain, A1 domain of activated vWF, vWF A3 domain.
D2 (claim 5) discloses an antibody that binds selectively to the active conformation of human von Willebrand Factor (vWF) and wherein said antibody inhibits the binding of vWF to platelets (claim 1) and wherein said antibody may be a single chain variable region immunoglobulin (ScFv) fragment (claim 2).

Neither D1 not D2 discloses the particular CDR sequence combination SEQ ID 15, with SEQ ID NO 23 with SEQ ID NO 33. This subject-matter is therefore regarded as novel but not inventive.
Both D1 and D2 relate to the same general concept (see Item IV) as the presently

claimed subject-matter. It should be noted that in cases such as the present one where the single general concept lacks novelty and inventive step, the novel embodiments cannot initially be regarded as being inventive in the absence of a special effect for the particular embodiment(s).